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19 April 2007

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: GAUCHER DISEASE DRUGS AND METHODS OF IDENTIFYING SAME

(57) Abstract: A method of identifying a compound capable of correcting an impaired enzymatic activity of a mutant glucocerebrosidase molecule, the method comprising: (a) obtaining a first set of structure coordinates, the first set of structure coordinates defining a 3D structure of a glucocerebrosidase molecule capable of displaying normal enzymatic activity or a portion thereof; (b) computationally generating using the first set of structure coordinates a second set of structure coordinates, the second set of structure coordinates defining a predicted 3D structure of the mutant glucocerebrosidase molecule or a portion thereof; and (c) computationally identifying, using the second set of structure coordinates, a compound capable of interacting with the mutant glucocerebrosidase molecule in such a way as to correct the impaired enzymatic activity thereof, thereby identifying the compound capable of correcting the impaired enzymatic activity of the mutant glucocerebrosidase molecule. A glucocerebrosidase preparation comprising a population of glucocerebrosidase molecules: (i) has an amino acid sequence at least 95 percent homologous to an amino acid sequence set forth by SEQ ID NO: 1 or 8; (ii) is glycosylated at, or has an aspartatic acid residue at, glycosylation residue 1 of said amino acid sequence, and (iii) is independently unglycosylated at one or more glycosylation residues selected from the group consisting of glycosylation residues 2, 3 and 4 of said amino acid sequence.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL04/00335

A. CLASSIFICATION OF SUBJECT MATTER
IPC: **C12N 9/26(2007.01);A61K 38/00(2007.01),38/47(2007.01)**

USPC: 435/201;514/2;424/94.61
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 435/201; 514/2; 424/94.61

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
MEDLINE, AGRICOLA, CAPLUS, BIOSIS, WPIDS, EAST, GENBANK, GENPEPT, SWISS-PROT, EMBL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	ROEBBER, D. et al. Crystallization and preliminary X-ray analysis of recombinant human acid B-glucocerebrosidase, a treatment for Gaucher's disease. Acta Crystallographica Section D Biological Crystallography. February 2003, Vol D59, pages 343-344.	1-3, 5-6, 33-37, 57-75 ---------- 87-97

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search 14 December 2006 (14.12.2006)	Date of mailing of the international search report 17 JAN 2007
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	Authorized Officer David F. Steadman Telephone No. 571-272-1600

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL04/00335

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of any additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-8, 33-54, 57-75, 87-97, reciting Table 4 and SEQ ID NO:1

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-8, 33-54, 57-75, 87-97, drawn to the special technical feature of a composition of matter comprising a crystallized glucocerebrosidase, a method of crystallizing a glucocerebrosidase molecule, a glucocerebrosidase preparation, a pharmaceutical composition, and an article of manufacture.

Group II, claim(s) 9-22, drawn to the special technical feature of a method of identifying a compound.

Group III, claim(s) 23-32, 55, drawn to the special technical feature of a computing platform and a computer-readable medium.

Group IV, claim(s) 56, drawn to the special technical feature of a computer generated model.

Group V, claim(s) 76-86, drawn to the special technical feature of a method of producing a glucocerebrosidase preparation.

Group VI, claim(s) 98-109, drawn to the special technical feature of a method of increasing glucocerebrosidase activity in a cell.

Group VII, claim(s) 110-122, drawn to the special technical feature of a method of treating a disease.

If applicant elects the invention of Group I, applicant is further required under PCT Rule 13.1 to elect a single glucocerebrosidase from the following:

1) glucocerebrosidase of Table 4 and SEQ ID NO:1

2) glucocerebrosidase of Table 5 3) glucocerebrosidase of Table 6

4) glucocerebrosidase of Table 7 5) glucocerebrosidase of Table 8

6) glucocerebrosidase of Table 9 7) glucocerebrosidase of Table 10

8) glucocerebrosidase of SEQ ID NO:8

9) glucocerebrosidase of SEQ ID NO:16

If applicant elects the invention of Group II, applicant is further required under PCT Rule 13.1 to elect a single Table disclosing a first set of structural coordinates from the following Tables:

1) Table 4 - SEQ ID NO:1 2) Table 5 - SEQ ID NO:2

3) Table 6 - SEQ ID NO:3 4) Table 7 - SEQ ID NO:4

5) Table 8 - SEQ ID NO:5 6) Table 9 - SEQ ID NO:6

7) Table 10 - SEQ ID NO:7

and to elect a single Table disclosing a second set of structural coordinates from the following Tables:

8) Table 11 9) Table 12 10) Table 13

11) Table 14 12) Table 15 13) Table 16

14) Table 17 15) Table 18 16) Table 19

17) Table 20 18) Table 21 19) Table 22

If applicant elects the invention of Group III, applicant is further required under PCT Rule 13.1 to elect a single Table disclosing a set of structural coordinates from the following Tables:

1) Table 4 - SEQ ID NO:1 2) Table 5 - SEQ ID NO:2

3) Table 6 - SEQ ID NO:3 4) Table 7 - SEQ ID NO:4

5) Table 8 - SEQ ID NO:5 6) Table 9 - SEQ ID NO:6

7) Table 10 - SEQ ID NO:7

8) Table 11 9) Table 12 10) Table 13

11) Table 14 12) Table 15 13) Table 16

14) Table 17 15) Table 18 16) Table 19

17) Table 20 18) Table 21 19) Table 22

If applicant elects the invention of Group IV, V, or VI, applicant is further required under PCT Rule 13.1 to elect a single glucocerebrosidase from the following:

1) SEQ ID NO:1 2) SEQ ID NO:8

3) SEQ ID NO:16 The technical feature linking groups I-VII is a glucocerebrosidase polypeptide. The inventions listed as Groups I-VII do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

According to PCT Rule 13.2 and to the guidelines in Section (f)(i)(B)(1) of Annex B of the PCT Administrative Instructions, all alternatives of a Markush Group must have a common structure, which is a significant structural element. Although the glucocerebrosidase polypeptides of SEQ ID NO:1-7 or the structural coordinates of Tables 4-7 and 11-22 share a common structure, the polypeptides or structural coordinates are not regarded as being of similar nature because the shared common structure is not a significant structural element.

According to PCT Rule 13.2 unity of invention exists only when there is a shared same or corresponding special technical feature among the claimed inventions. the crystal of Group I, the computing platform of Group III, and the computer model of Group IV share no special technical feature as the crystal of Group I encompasses glucocerebrosidase polypeptides having structures that do not correspond to the structural coordinates of the computing platform of Group III and the computer model of Group IV.

According to PCT Rule 13.2 unity of invention exists only when the shared same or corresponding special technical feature is a contribution over the prior art. The inventions of Groups I-VII do not relate to a single general inventive concept because they lack the same or corresponding special technical feature. The technical feature of Group I is a crystal of a glucocerebrosidase, which is shown by Roeber et al. (*Acta Crystallogr D Biol Crystallogr* 59:343-344, 2003, abstract only) to lack novelty or inventive step because the abstract of the reference of Roeber et al. teaches a crystal of glucocerebrosidase and does not make it a contribution over the prior art.

In the absence of any response from Applicant, this Authority will establish the International Search Report based on the main invention, i.e., the claims of Group I, reciting the glucocerebrosidase of Table 4 and SEQ ID NO:1.